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10/573,023	03/22/2006	Yasushige Yonezawa	W1878.0229	4509
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DICKSTEIN SHAPIRO LLP 1177 AVENUE OF THE AMERICAS (6TH AVENUE) NEW YORK, NY 10036-2714			EXAMINER BORIN, MICHAEL L	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/573,023	<b>Applicant(s)</b> YONEZAWA ET AL.	
	<b>Examiner</b> Michael Borin	<b>Art Unit</b> 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 07 November 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 2-6, 14 and 15 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-6, 14 and 15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/07/2008 and 08/23/2006</u> .                               | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### **Status of Claims**

Claims 1-18 are pending.

Response to restriction requirement filed 05/19/2008 is acknowledged. Applicant elected, without traverse, Group II, claims 2-6,14,15. Claims 1,7<sup>1</sup>-13,16-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected groups.

### ***Information Disclosure Statement***

Applicants' Information Disclosure Statements filed 11/07/2008 and 08/23/2006 have been received and entered into the application. The information disclosure statements fail to comply in full with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The reference of Sakuma and Nakada which was specifically requested in communication mailed 08/22/2008 has not been received. Although it seems that document titled " Development of QM/MM System for Large-scaled

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<sup>1</sup> Examiner acknowledges that claim 7 was inadvertently left out in the restriction requirement and not restricted to a particular group, and agrees with Applicants that claim 7, which is drawn towards a device, was intended to be restricted to Group III.

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Biological Molecular Calculations” submitted with IDS of 11/07/2008 is relevant to said publication of Sakuma and Nakada, it has different authors (Sakuma, Nakata, Shimada, Takada) and no date and reference for said printout is provided.

### ***Claim Objections***

Claim 2 is objected to because of the following informalities: It seems that the term “apace” in “MM apace” is supposed to be “MM space” . Appropriate correction is required.

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 2,3 are directed to one superficial QM region, whereas claim 4 addresses a plurality of superficial QM regions. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

### ***Claim Rejections - 35 USC § 112, second paragraph.***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-6,14,15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

A. Claim 2: the first step of the method requires division of QM space into superficial and non-superficial regions. Neither the metes and bounds of the term “superficial QM region”, nor particular active method steps resulting in the division of the QM space are defined; therefore, it is not clear what and how is being done on this method step. please clarify via clearer claim language.

B. Claim 2: The method is based on term “based on empirical potential” for superficial QM region. The term empirical implies derived from experiment and observation rather than theory (see

<http://wordnetweb.princeton.edu/perl/webwn?s=empirical>

for example.

However, it does not seem that the method as described in the specification addresses any terms derived from experiment and observation. See p. 16, for example. Thus, the meaning of the term “empirical” is not clear.

C. Claim 3: The term “inputting a parameter” is not clear. Entering into which method step, or which equation?

D Claim 4 addresses “a parameter”. It is not clear which parameter is meant.

E. Claim 5: It is not clear what is the “wave function” addressed in the claim and which method step representing such wave function contributes to.

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F. Claim 6: The claim addresses further steps of “molecule structure optimization” and “time evolution calculation”. The meaning of these steps is not clear - what optimization is meant, and evolution of which time is performed, as well as it is not clear how these steps contribute to the method as claimed in the base claims. Further, the nature of “time expansion calculation” addressed in the claim is also unclear.

***Claim Rejections - 35 U.S.C. § 101***

The following is a quotation of the 35 U.S.C. § 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2-6,14,15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 2-6,14,15 are drawn to molecular simulation method for dividing a molecule or a part of molecule to be simulated into a quantum mechanics (QM) and molecular mechanics (MM) space. The claims do not recite any physical transformation step, nor they recite a tie to another category of invention.

To qualify as a statutory process, the claims should positively recite the other statutory class (the thing or product) to which it is tied, for example by identifying the apparatus that accomplishes the method steps, or positively recite the subject matter that is being transformed, for example by identifying the material that is being changed to a different state or thing. In the instant case, claims do not recite any physical

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transformation step. Further, there is no step in the claims that recites a tie to another category of invention. Therefore, the claims are drawn to non-statutory subject matter for failing to recite a step that ties the method to another category of invention.

A claimed process is patent-eligible under § 101 if it is tied to a particular machine or apparatus, or it transforms a particular article into a different state or thing. Thus, the machine-or-transformation test is a two-branched inquiry: an applicant may show that a process claim satisfies § 101 either by showing that his claim is tied to a particular machine, or by showing that his claim transforms an article. See *In re Bilski* (Fed. Cir., October 30, 2008). The use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility. Further, the involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity.

Applicants' process is neither tied to a particular machine or apparatus, nor it transforms a particular article into a different state or thing. Thus, the claims fail the machine-or-transformation test and is not drawn to patent-eligible subject matter.

Further, there is no practical application to produce a real-world result as a result of the method as claimed. A tangible result requires that the claim must set forth a practical application to produce a real-world result. In the instant case, there is no tangible output of a result of the claimed method.

***Claim Rejections - 35 USC § 112, first paragraph.***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-6,14,15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standards by which a specification is judged to be "enabling" were set forth in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988). Some of the standards taken under consideration are: 1) the state of the prior art; 2) the predictability or lack thereof in the art; 3) the amount of direction or guidance present; 4) the presence or absence of working examples; and 5) the breadth of the claims. The following is an analysis of some of these factors in relation to this application.

The method requires dividing QM space into QM region and QM superficial region. The metes and bounds of the "superficial" are not clear and thus, it is not clear

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how to practice the invention as claimed. there are no working examples demonstrating appears in the description of Fig. 4 (see p/ 18, last full paragraph), arbitrarily pointing out at C-C bond in the second amino acid residue from the left. p. 9, top, identifies what superficial QM region is but does not guide how to determine it.

Further, the method is not enabled because, apart from the theoretical discussion, there is no demonstration of applicability of the method. field et al. teach that there are limits to the use of QM/MM method and it is important to test its applicability to each particular use. Thus, the art is deemed unpredictable for a traditional QM/MM method, much less for the method as claimed.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

***Claim Rejections - 35 USC § 102.***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 is rejected under 35 U.S.C. 102(b) as anticipated by Field et al (Journal of Computational Chemistry ,Vol. 11, p . 700-733, 1990; see IDS)

Field teaches method of a combined quantum mechanical and molecular mechanical potential for molecular dynamics simulations. For the quantum mechanical calculations semiempirical methods of the MND0 and AM1 type are used, while the molecular mechanics part is treated with the CHARMM force field. See Abstract. Field teaches that In cases with a relatively large number of QM atoms, it may be advantageous to use hybrid schemes and that for ab initio QM or density functional methods, some method to minimize the number of quantum mechanical calculations may be needed. For example, the QM energy and forces could be calculated every few steps and for intermediate points an estimate of the energy could be made using an extrapolation method or perturbation theory. See p. 706, right column, first paragraph.

In the example above demonstrating reduction of amount of atoms to be calculated by QM algorithm by skipping every few atoms/steps, Field teaches method as instantly claimed because skipping intermediate atoms will inherently include, to some extent, a boundary area between MM and QM areas, and, therefore, the calculation of total QM energy will be made as instantly claimed.

Claim 2 is rejected under 35 U.S.C. 102(b) as anticipated by Zhang et al. (Zhang et al. J. Chem. Phys. 110, 46-54,1999)

Zhang et al teach a pseudobond approach for combined *ab initio* quantum mechanical and molecular mechanical calculations QM/MM. The method introduces a free-valence boundary atoms (Yps) on the frontier between MM and QM regions (i.e. superficial QM area). The pseudobond formed between a Yps atom and a boundary atom of the active part mimics the original covalent bond with similar bond length and strength, and similar effects on the rest of the active part. The effective core potential for the boundary atoms (Yps) depends on the basis set used in the QM calculations, but not on the MM force fields. There are no additional atoms added and no double counting of the interactions. The boundary region between the active art and the environment part is explicitly and well treated without any energy and force corrections or constraints. See page 48, and paragraph bridging pages 52 and 53.

Thus, the method of Zhang et al is viewed as including empirical potential for superficial QM area.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./  
Primary Examiner, Art Unit 1631

mlb